# GUIDANCE[1]

# GLYBURIDE

# *IN VIVO* BIOEQUIVALENCE

# AND *IN VITRO* DISSOLUTION TESTING

## I. INTRODUCTION

### A. Clinical Usage/Pharmacology

Glyburide is an oral antidiabetic agent which lowers blood glucose level. It is currently approved for controlling blood glucose in non-insulin-dependent diabetes mellitus (NIDDM) patients whose blood glucose cannot be controlled by diet alone. Glyburide acts mainly by stimulating endogenous insulin release from beta cells of pancreas.

Glyburide is usually administered as a single daily dose each morning with breakfast or with the first main meal. The recommended initial adult dose of glyburide is 2.5 to 5 mg daily. The maximum recommended single daily dose is 10 mg. Some patients who require more drug than 10 mg daily may have a more satisfactory response when glyburide is administered in two divided doses. The maximum recommended total daily dose under these circumstances is 20 mg. The optimum dosing

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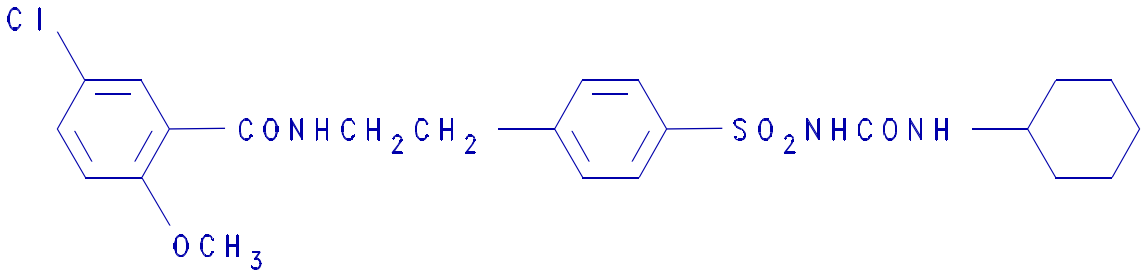
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

regimen of glyburide for each patient is obtained by titration. Glucose (urinary and blood) and blood glycosylated hemoglobin (Hb A1c) are used as the indicators of effective therapy (1). The most commonly observed adverse effects after administration of glyburide are dizziness or lightheadedness which are due to hypoglycemia (1,2).

The drug is currently marketed as immediate release tablets in 1.25 mg, 2.5 mg and 5 mg strengths by Upjohn and by Hoechst Roussel under the brand names Micronase $^{R}$ and Diabeta $^{R}$, respectively (3).

## B. Chemistry

Glyburide is a sulfonylurea, antidiabetic agent which is structurally similar to acetohexamide and glipizide (1,4). It is sparingly soluble in water with a molecular weight of 494 and pKa of 5.3 (4). The structural formula is shown below :




## C. Pharmacokinetics

Glyburide is rapidly and completely absorbed after oral administration. As there is no significant first pass metabolism, 100% of the oral dose is bioavailable (5). After oral administration, glyburide reaches peak plasma or serum concentration within 4 hours and exhibits an elimination half-life of 10 hours (1). More recently, a terminal elimination rate of 1.4 - 5 hours has been reported(6). Glyburide concentration-time curves in plasma exhibit biphasic elimination (1,2). Primary metabolites of glyburide are hydroxylation products (4-trans-hydroxy and 3-cis-hydroxy derivatives) that are inactive (1,6) and are excreted in urine (50%) and in feces (50%) via bile (1,6). Plasma levels of glyburide in the range of 20

to 90 ng/ml has been reported as therapeutically effective in the literature (7).

## II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

### A. Product Information

1. FDA Designated Reference Product: 5 mg Micronase® Tablet (Upjohn).

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger .

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

### B. Types of Studies Required

1. A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting condition comparing equal doses of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence, crossover, limited food effects study comparing equal doses of the test under fasting condition as well as the test and reference products when administered immediately following a standard breakfast.

### C. Recommended Protocol for Conducting a Single Dose Bioequivalence Study under Fasting Condition

*Objective:* To compare the rate and extent of absorption of a generic formulation with that of a

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[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

reference formulation when given in equal labeled doses.

*Design (Single Dose):* The study design is a single dose, two-treatment, two-period, two-sequence crossover with a one week washout period between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

*Facilities:* The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

*Selection of Subjects:* The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers 18 to 50 years of age and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

*Procedures (Single Dose)*[3]*:* Following an overnight fast of at least 10 hours, subjects should be

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[3] Glipizide(5 & 10mg) and glyburide(1.25, 2.5, & 5mg), the second generation sulfonylurea, antidiabetic agents, are comparatively more potent than tolbutamide(250 & 500mg) and tolazamide(100, 250 & 500mg). The difference in the potency is obvious from the dosage strengths of tablets for these drug products. Therefore, in a fasting bioequivalence study involving normal subjects, hypoglycemic events occur more frequently with glipizide and glyburide than with tolbutamide and tolazamide (2). Moreover, in case of glipizide, the hypoglycemic episodes in normal subjects participating in a fasting bioequivalence study were fewer when the glucose was given to subjects every 15 minutes than when it was given every 30 minutes (2). In a study with such a design, measurement of plasma glucose is not necessary since it will not reflect the pharmacodynamic end point. However, such design is preferable to the usual fasting study design to ensure the welfare of subjects and to avoid excessive drop out rate.

administered a single dose (1x5 mg tablet) of the test or reference product with 240 ml 20% glucose solution in water. Every subjects should be given 60 ml 20% glucose solution in water, post dose, every 15 minutes for 4 hours.

*Restrictions:* Study volunteers should observe the following restrictions:

a. No additional drinking water or fluids (except for that described above which is needed for drug dosing) is allowed from 1 hour predose to 1 hour postdose.

b. Subjects should fast for at least four hours after administration of the test or reference treatment( 20% glucose water is allowed. See procedures.). All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medication beginning two weeks and OTC drug beginning one week before drug administration until after the study is completed.

*Blood Sampling (Single Dose):* Venous blood samples should be collected pre-dose (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 hours post-dose. Plasma should be separated promptly and immediately frozen until assayed. Following a one week washout period, subjects should begin Study Phase Two.

*Analytical Methods:* The active ingredient should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard

curve and Q.C. chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

*Statistical Analysis of Pharmacokinetic Data (Plasma):* See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

*Clinical Report and Adverse Reactions:* Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

## D. Limited Food Effects Study

The limited food effects study should be performed in the same manner as the single-dose fasting study, with the following exceptions:

*Procedures:* Equal number of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design. Each subject will receive the following treatments:

*Treatment 1:* Generic Product, [1x5 mg tablet] administered after standard breakfast [4]

*Treatment 2:* Reference (Micronase [R]) Product, [1x5 mg Tablet] administered after standard breakfast [4]

*Treatment 3:* Generic Product, [1x5 mg Tablet] dosed fasted

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[4] Each subject should consume a standardized, high fat content meal consisting of:

One buttered English muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

Following a ten hour fast, the subjects receiving the treatments under fed condition should be served a standard breakfast [3]. The subjects should have thirty minutes to finish the entire breakfast, and then should immediately receive Treatment 1 or 2, with 240 ml of 20% glucose solution in water. Subjects receiving the treatment under fasting condition should have Treatment 3, with 240 ml 20% glucose solution in water. The lots of the test and reference products used in this limited food effect study should be the same as the lots used in the fasting study, above. Each subject in all three Treatments should receive 60 ml of 20% glucose solution in water post dose every 15 minutes for four hours. No food should be allowed for at least 4 hours post-dose and no additional water or fluids should be allowed from 1 hour predose to 1 hour postdose. Subjects should be served scheduled standardized meals throughout the study.

*Statistical Analysis:* In general, no food effect will be assumed if the $AUC_{0-T}$, $AUC_{0-\infty}$, and $C_{max}$ mean values for the generic product administered under fed condition (Treatment 1) are within 20% of the respective mean values for the reference product administered under fed condition (Treatment 2).

*Retention of Samples:* The applicant is supposed to retain about 200 drug dosage units each of the test and reference drug products from the lots used in *in vivo* bioequivalence study. The applicant should refer to the section 320.32 of 21CFR for the detail information.

## III. *IN VITRO* TESTING REQUIREMENTS

There is currently no official monograph on a glyburide drug product in USP XXII and therefore, no USP dissolution testing method is available. A tentative method recommended by FDA is described below.

### A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test and reference products. Wherever applicable, the lots of the dosage units used in the *in vitro* dissolution testing should be the same as the lots of the dosage units used in the *in vivo* bioequivalence

study. The following method and tolerances are recommended:

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| Apparatus: | USP XII apparatus 2 (paddle) |
| RPM: | 75 |
| Medium: | 0.05M Borate buffer pH 9.5 |
| Volume: | 500 ml |
| Sampling Times: | 15, 30, 45 and 60 minutes |
| Tolerance (Q): | NLT 70% in 45 minutes |
| Analytical: | Validated method |

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

**B. Content Uniformity Test**

Content uniformity testing on the test product lots should be performed as described in USP XXII.

## IV. WAIVER REQUIREMENTS

**A.** Waiver of *in vivo* bioequivalence study requirements for the 1.25 mg and 2.5 mg tablets of the generic product may be granted as per 21 CFR 320.22(d)(2) provided both of the following conditions are met:

1. The 1.25 mg and 2.5 mg tablets are proportionally similar in both active and inactive ingredients to the 5 mg tablet which has been shown *in vivo* to be bioequivalent to the listed reference product.

2. The 1.25 mg and 2.5 mg tablets of the generic product meet the *in vitro* dissolution testing requirements.

## V. REFERENCES


1. Physician's Desk Reference. 46th ed. Montvale, NJ: Medical Economics Company, 1992:2350-1.

2. Data on file with the Division of Biopharmaceutics and the Division of Bioequivalence.

3. Approved Drug Products with Therapeutic Equivalence Evaluation (Orange Book). 12th ed. Washington DC: US Dept of HHS, 1992:3-133.

4. Budaveri S, O'Neil MJ Smith A Heckelman PE. The Merck Index 11th ed. New Jersey: Merck and Co. Inc, 1989:703.

5. Neugebauer G, Betzien G, Hrstka V, Kaufmann B, von-Mollendorff E, Abshagen U. Absolute bioavailability and bioequivalence of glibenclamide (semi-euglucon). Int J Clin Pharmacol Ther Toxicol 1985;23(9):453-60.

6. Marchetti P, Giannarelli R, di Carlo A, Navalesi R. Pharmacokinetic Optimization of oral hypoglycemic therapy. Clin Pharmacokinet 1991;21(4):308-17.

7. Groop LC, Barzilai N, Ratheiser K, Luzi L, Wahlin-Boll E, Melander A, DeFronzo RA. Dose-dependent effect of glyburide on insulin secretion and glucose uptake in humans. Diabetes Care 1991;14(8):724-7.

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